

Molecular analysis of the PI3K-AKT pathway in uterine cervical neoplasia: Frequent PIK3CA amplification and AKT phosphorylation

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Abstract

Uterine cervical carcinogenesis is probably dependent on cellular genetic damage in addition to the integration of high-risk HPV DNA in the epithelial cell genome. Gain of chromosome 3q24-29 is commonly observed in cervical neoplasia. The putative oncogene PIK3CA located in this region encodes a phosphatidylinositol 3-kinase (PI3K). In a process reversed by PTEN, PI3K generates inositol phospholipids that trigger AKT phosphorylation, which in turn effects tumor driving signals. We studied 46 specimens of formalin-fixed, paraffin-embedded cervical neoplastic tissue. The activation state of the PI3K-AKT pathway was assessed immunohistochemically using an antibody with specificity towards serine 473-phosphorylated AKT. AKT phosphorylation was found in 39 out of 46 examined specimens. To examine the possible molecular basis for this activation, we searched for PIK3CA amplification using quantitative real-time polymerase chain reaction. PIK3CA gene copy number was estimated to be 3 or more in 28 out of 40 successfully examined cases. Further, a PTEN mutation analysis of all 9 PTEN exons was carried out, but except for 1 metastasis with an exon 9 V369I heterozygosity, all cases showed normal PTEN sequence. Immunohistochemical staining for PTEN was strong in all lesions. In conclusion, an increased activation state of AKT kinase appears to be present in cervical carcinogenesis, and may be accounted for by PIK3CA amplification, whereas PTEN mutation seems to be of little importance. © 2005 Wiley-Liss, Inc.

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